PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	See form PCT/ISA/210
Applicant's or agent's file reference BLOcp263-107	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/FR2005/000656	17.03.2005	17.03.2004

International Patent Classification (IPC) or both national classification and IPC
C12Q1/68

Applicant
COMMISSARIAT A L'ENERGIE ATOMIQUE

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/EP	Authorized officer
Facsimile No.	Telephone No.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/FR2005/000656

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☒ in written format

      ☒ in computer readable form

   c. time of filing/furnishing

      ☒ contained in the international application as filed.

      ☒ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/FR2005/000656

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 7-11,29-36 (in part)

because:

☐ the said international application, or the said claims Nos. _____
relate to the following subject matter which does not require an international preliminary examination (*specify*):

See supplemental sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 7-11,29-36 (in part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/FR2005/000656

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-11, 15-22, 24-26	YES
	Claims	12-14, 23, 27-36	NO
Inventive step (IS)	Claims	1-11, 15-22, 24-26	YES
	Claims	12-14, 23, 27-36	NO
Industrial applicability (IA)	Claims	1-36	YES
	Claims		NO

2. Citations and explanations:

Reference is made to the following documents:

D1: CHEN CHI-HONG B ET AL: "Inhibition of heregulin signaling by an aptamer that preferentially binds to the oligomeric form of human epidermal growth factor receptor-3". PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 100, no. 16, 5 August 2003 (2003-08-05), pages 9226-9231, XP002303440 ISSN: 0027-8424

D2: WO 2004/011680 A (ARCHEMIX CORP; DIENER JOHN L (US); EPSTEIN DAVID (US); WILSON CHARLES) 5 February 2004 (2004-02-05)

D3: WO 99/51777 A (BUNSEN RUSH LAB INC; LERNER MICHAEL R (US)) 14 October 1999 (1999-10-14)

1 Claim 1

Document D1, which is considered to be the prior art closest to the subject matter of claim 1, describes (the references between parentheses apply to this document): a method for identifying ligands or aptamers specific for a membrane receptor tyrosine kinase (HER3, abstract) expressed by cells. The method comprises at least the following steps

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

a) bringing a mixture of nucleic acids into contact with said membrane receptor tyrosine kinase,

b) recovering a subset of nucleic acids which bind with the receptor,

c) amplifying said nucleic acids and identifying them (methods).

Therefore, the subject matter of claim 1 differs from D1 in that it comprises 2 counterselection steps: 1) with a non-activated form of the receptor, or without the receptor, and 2) with a receptor mutated in the intracellular portion. Also, the selection step uses a receptor which is in an activated form due to the existence of a mutation in the extracellular domain. The technical effect of these differences is that the method makes it possible to identify aptamers or ligands for receptors in an activated form linked with an extracellular mutation. The subject matter of claim 1 is thus novel (PCT Article 33(2)).

The problem that the present invention is intended to solve can thus be considered to be the provision of a more specific method for identifying aptamers of an activated form of a tyrosine kinase membrane receptor.

The solution to this problem, as proposed in **claim 1** of the present application, is considered to involve an inventive step (PCT Article 33(3)), for the following reasons: D2 describes a counterselection step (page 12), but using one or more molecules different from the target molecule and not mutant forms. D3 describes the use of membrane receptor mutants, but the mutants are not used in a counterselection step. There is no document in the

prior art which suggests that two different counterselection steps will solve the stated problem.

Claims 2-6 are dependent on claim 1 and as such also meet the requirements of novelty and inventive step of the PCT.

2 Claim 7

Taking into account the restrictions indicated above, the aptamers having the nucleotides of SEQ ID NOS 22, 25, and 31-33 are novel.

These aptamers have a similarity with the aptamers described in D4 (70-80% identity). The aptamers of SEQ ID NOS 22, 25, and 31-33 differ from D4 in that the aptamers have a different specificity, since they have an affinity with respect to at least one a membrane receptor tyrosine kinase mutated in the extracellular domain.

The problem that the present invention is intended to solve can thus be considered to be the provision of aptamers of an activated form of a tyrosine kinase membrane receptor.

There is no document in the prior art which suggests which modifications in the aptamers of D4 will be necessary for this different specificity.

Claims 7-11 limited to the aptamers corresponding to SEQ ID NOS 22, 25, and 31-33 are considered to involve an inventive step (PCT Article 33(3)).

3 Claims 12-14, 23, 27-36

D4 describes aptamers having the formula R-R-R2, in which R represents SEQ ID NO. 1, R2 represents a fragment of 21 nucleotides of SEQ ID NO. 2, and R represents a random

sequence of 50 nucleotides (e.g. SEQ ID NOS 201, 213, 215, 259 of D4).

The riboses of the purines bear a hydroxyl function on the carbon in the 2'-position, while the riboses of the pyrimidines bear a fluorine atom in the 2'-position.

These aptamers can be used in pharmaceutical compositions (page 7). Also, the use of an aptamer which has both a binding capacity and an inhibitory action with respect to the receptor for the screening of products which interact is described in D4 (page 7). The subject matter of claims 12, 13, 14, 23, and 27-36 is not novel (PCT Article 33(2)).

4 Claims 16-22, 24-26

A reasoning equivalent to that for claims 7-11 is applicable for claims 16-22 and 24-26. The subject matter of claims 16-22 and 24-26 is considered to involve an inventive step (PCT Article 33(3)).

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box III

The use of functional definitions in claims (as in claims 7 to 11, 12-22) is sometimes admissible. However, in the case of claims 7-11, the intended limitations are therefore not clear from these claims, contrary to the requirements of PCT Article 6.

A person skilled in the art ***cannot*** implement a definition of the subject matter claimed since the compounds claimed as such (claim 7) or appearing in the use claims potentially harbour an unlimited number of structures; there is in fact no limit to the structural variations of the compounds which could be obtained by means of a method of identification as in claims 1-6, the latter even encompassing compounds which have not yet been synthesized. Claims 7 to 11 thus lack clarity.

In addition, the examination would never be able to determine whether such claims differ from the prior art since, in order to do this, it would be necessary to test all known and unknown aptamers in order to determine whether they have an affinity for the receptor X or whether they have an agonist or antagonist activity with respect to the latter. The non-identification of the scope of the claim is thus an additional reason for reaching the conclusion of lack of clarity (PCT Article 6). Furthermore, since it is impossible for the public to determine whether an activity or a specific product is encompassed by such a claim, the latter lacks clarity pursuant to PCT Article 6.

Therefore, the search and the written opinion with regard to claims 7-11 were limited to the aptamers corresponding

Supplemental Box

to SEQ ID NOS 22, 25 and 31-33. In addition, claims 28-32 are treated in this manner.

Claims 12-22 use a functional definition, but add structural features thereto.